Amendments to the claims

Claims 6-7 are amended according to the restriction requirement; claim 6 is also amended to overcome the 35 U.S.C. §112, second paragraph rejection. No new matter has been added.

The 35 U.S.C. §112, second paragraph rejection

Claims 6-7 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claim 6 is amended to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as helpfully suggested by the Examiner. Accordingly, Applicants respectfully request that the rejection of claims 6-7 under 35 U.S.C §112, second paragraph, be withdrawn.

The 35 U.S.C. §102(e) rejection

Claims 6 and 7 are rejected under 35 U.S.C. §102(e) as being anticipated by **Hallahan** *et al.*, U.S. Pat. No. 6,159,443. This rejection is respectfully traversed.

Hallahan teaches a method of targeting a tissue for delivery of an active agent in combination with exposing the tissue to ionizing radiation, where the active agent comprises a platelet. The "delivery vehicles" taught by **Hallahan** have the ability to

preferentially bind to activated platelets (column 3, lines 49-65). In **Hallahan**, expression of cell adhesion molecules on the surface of vascular endothelial cells is used as a means of attachment of the platelets to the endothelial cells, in which a "loaded platelet" has the active agent bound to its surface, thereby delivering the active agent to the vascular endothelial cell (column 2, lines 18-26).

The method taught by **Hallahan** is different from the method of Applicants' claims 6-7. The present claims are drawn to a method of treating a pathophysiological state by irradiating the target tissue, and administering a biodegradable particle comprising antibodies or antibody fragments that bind to P-selectin or ICAM-1 on the surface of an endothelial cell, and a pharmaceutical. It is therefore the biodegradable particle itself that comprises the element that binds to the cell adhesion molecule on the endothelial cell surface. Applicants' method differs from the teachings of **Hallahan**, where it is the platelet that binds to the cell adhesion molecule such as P-selectin on the endothelial cell surface; any delivery vehicle containing an active agent that may be used in addition to the platelet is bound to the platelet, and does not bind to a cell adhesion molecule on the endothelial cell surface (column 3,

lines 50-65). Additionally, **Hallahan** does not teach a biodegradable particle bearing antibodies specific to ICAM-1.

Hallahan therefore does not anticipate claims 6-7, because **Hallahan** does not teach Applicants' claimed method. Accordingly, Applicants respectfully request that the rejection of claims 6-7 under 35 U.S.C. §102(e) be withdrawn.

The 35 U.S.C. §103(a) rejection

Claims 6 and 7 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Hallahan** *et al.*, U.S. Pat. No. 6,159,443, in view of the fact disclosed in the specification on pages 4, lines 15-20; 5, lines 1-5; and 10, lines 12-20, and **Mastrobattista** *et al.*, *Biochim. Biophys. Acta*, 1999, 1419: 353-363). This rejection is respectfully traversed.

The method of claims 6 and 7 is not obvious over **Hallahan** in view of the specification and **Mastrobattista**, because the cited references do not provide the necessary teaching or suggestion to combine the elements of the claimed method.

The specification describes the increase in expression of cell adhesion molecules on the surface of endothelial cells in response

to radiation, and that it would be ideal to deliver chemotherapeutic drugs specifically to the irradiated tissues. The method taught by **Hallahan**, as described above, attaches a delivery vehicle comprising an active agent to a platelet, where the platelet acts to target delivery of the active agent to endothelial cells by binding to a cell surface adhesion molecule induced by irradiation of the target tissue. **Mastrobattista** teaches liposomes bearing antibodies that bind to ICAM-1 expressed on the surface of cells, where such liposomes can be used as carriers to target delivery of anti-inflammatory drugs to sites of inflammation characterized by increased ICAM-1 expression. **Mastrobattista** does not teach the use of irradiation to increase the expression of cell adhesion molecules in the cells of a target tissue.

There is therefore no suggestion or teaching among the references to combine irradiation of a target tissue with administration of a biodegradable particle comprising an antibody or antibody fragment and a pharmaceutical, in order to deliver the pharmaceutical to the target tissue by binding of the particle via the antibody to P-selectin or ICAM-1 expressed on the surface of an endothelial cell. Accordingly, Applicants respectfully request that the rejection of claims 6-7 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed October 22, 2002. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: Jan 13, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend claim 6 to read as follows:

6. (amended) A method of treating a pathophysiological state in an individual in need of such treatment, comprising the steps of:

irradiating a target tissue or organ in said individual; and

administering to said individual ~~the biomolecular carrier of claim 1~~ a biodegradable particle comprising antibodies or antibody fragments that bind to P-selectin or ICAM-1 expressed on an endothelial cell, and a pharmaceutical.

Please amend claim 7 as follows:

7. (amended) The method of claim 6, wherein said pathophysiological state is selected from the group consisting of cancer, ~~arteriovenous malformations (AVM), macular degeneration and restenosis~~.